Claims

1. A method to enhance bone formation or to treat pathological dental conditions or to treat degenerative joint conditions in a vertebrate animal, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of a compound that inhibits the activity of NF-κB or that inhibits proteasomal activity or that inhibits production of proteasome proteins wherein the compound does not inhibit the isoprenoid pathway.

2. The method of claim 1, wherein the compound inhibits proteasomal activity or inhibits production of proteasomal proteins.

3. The method of claim 2, wherein the compound inhibits the chymotrypsin-like activity of the proteasome.

4. The method of claim 3, wherein the compound is a peptide having at least 3 amino acids and a C-terminal functional group that reacts with the threonine residue of the chymotrypsin-like catalytic site of the proteasome.

5. The method of claim 4, wherein the c-terminal functional group is selected from the group consisting of an epoxide, a $-B(OR)_2$ group, a $-S(OR)_2$ group and a -SOOR group, wherein R is H, an alkyl (C_{1-6}) or an aryl (C_{1-6}).

6. The method of claim 5, wherein the functional group is an epoxide that forms a morpholino ring with the threonine residue of the chymotrypsin-like catalytic site of the proteasome.

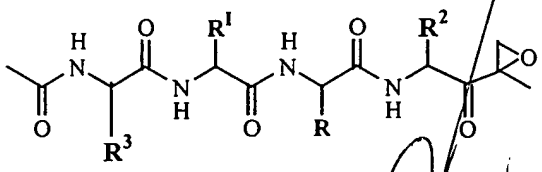
7. The method of claim 3, wherein the peptide is a peptide α', β'-epoxyketone.

8. The method of claim 7, wherein the peptide α', β'-epoxyketone has at least 4 amino acids.

9. The method of claim 7, wherein the c-terminus amino acid of the peptide α', β'-epoxyketone is a hydrophobic amino acid.

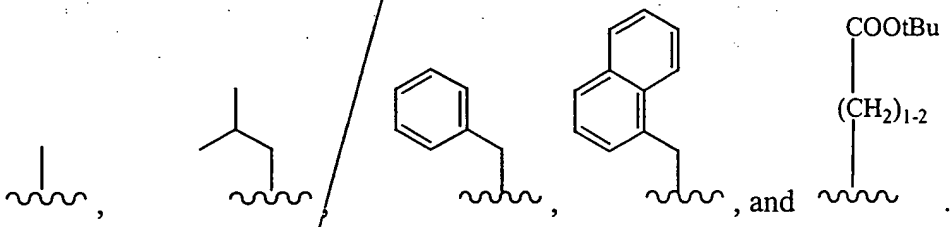
10. The method of claim 9, wherein the hydrophobic amino acid is leucine or phenylalanine.

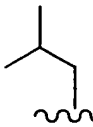
11. The method of claim 7, wherein the peptide α', β'-epoxyketone has the following formula:

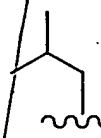
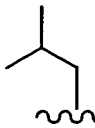


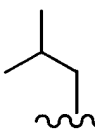
wherein each of R, R^1, R^2 and R^3 is a hydrophophic substituent.

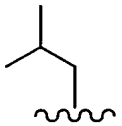
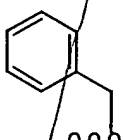
12. The method of claim 11 wherein each of R, R^1, R^2 and R^3 is independently selected from the group consisting of

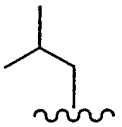
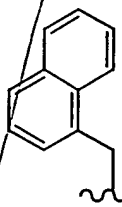


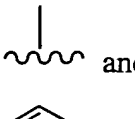
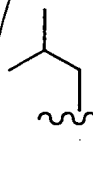
13. The method of claim 11, wherein R^2 and R^3 are  and the compound is selected from the group consisting of

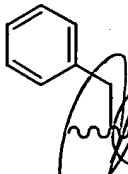
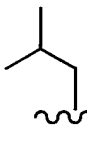
compound 1 (R^1=  and R= ),

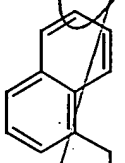
compound 2 (R^1=  and R= ),

compound 3 (R^1=  and R= ),

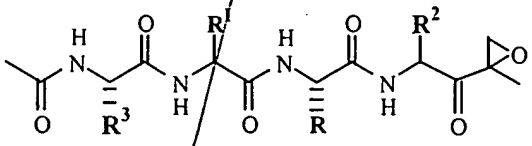
compound 4 (R^1=  and R= ),

compound 5 (R^1=  and R= ),

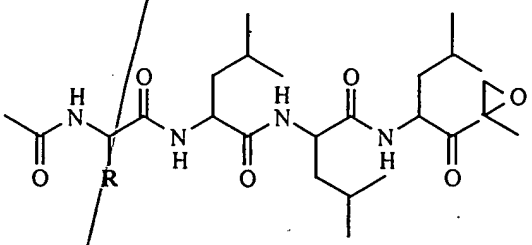
compound 6 (R^1=  and R= ) and

compound 7 (R^1=  and R= ).

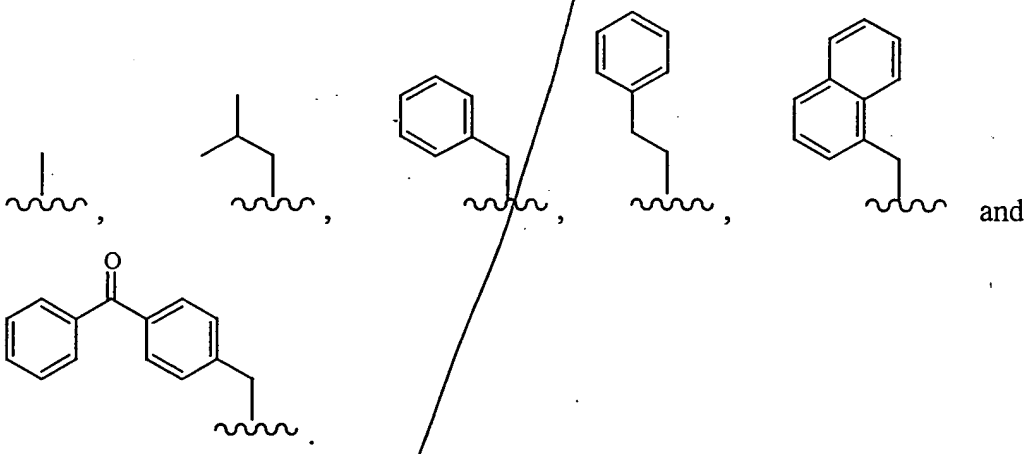
14. The method of claim 11, wherein the peptide α', β'-epoxyketone has the following stereo-configuration:



15. The method of claim 7, wherein the peptide α', β'-epoxyketone has the following formula:

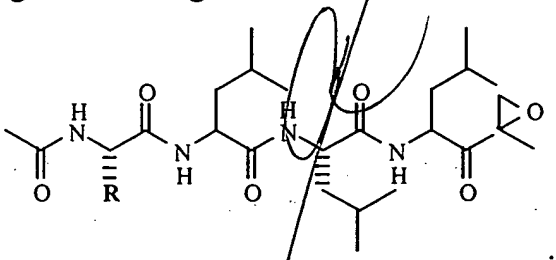


wherein R is selected from the group consisting of

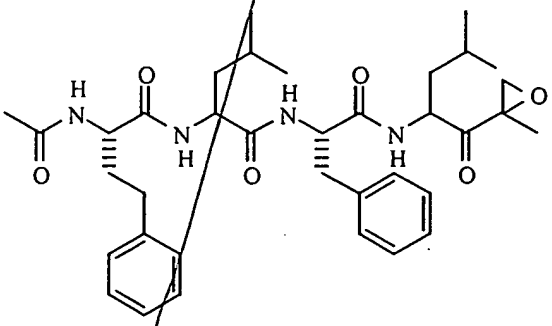


and

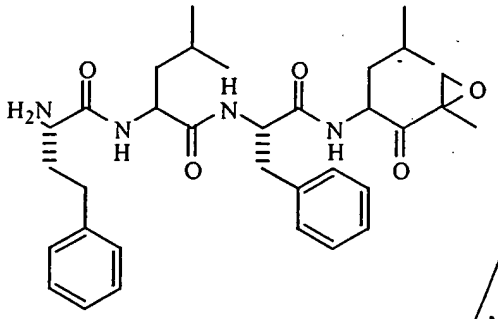
16. The method of claim 15, wherein the peptide α', β'-epoxyketone has the following stereo-configuration:



17. The method of claim 16, wherein the peptide α', β'-epoxyketone is

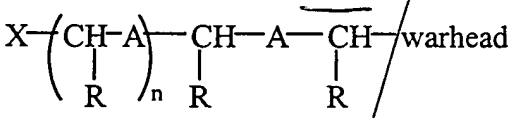


18. The method of claim 3, wherein the compound is selected from the group consisting of



, epoxomicin, PS-341, NLVS, PSI epoxide, lactacystin, PTX and a peptidyl aldehyde.

19. The method of claim 3, wherein the compound has the following formula:



,

wherein the warhead reacts irreversibly with the catalytic chymotrypsin site of the proteasome;

A is independently CO-NH or isostereomer thereof;

R is independently a hydrocarbyl;

X is a polar group; and

n = 0-2.

20. The method of claim 19, wherein R contains a substituted group selected from the group consisting of a halo group, -OR, -SR, $-NR_2$, =O, -COR, -OCOR, -NHCOR, $-NO_2$, -CN, and $-CF_3$.

21. The method of claim 19, wherein X is protected.

22. The method of claim 1, wherein the subject is characterized by a condition selected from the group consisting of osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation.

23. The method of claim 1, which further comprises administering to the subject one or more agents that promote bone growth or that inhibit bone resorption.

24. The method of claim 23, wherein the agents are selected from the group consisting of bone morphogenetic factors, anti-resorptive agents, osteogenic factors, cartilage-derived morphogenetic proteins, growth hormones, estrogens, bisphosphonates, statins and differentiating factors.

25. A method to treat a mammalian subject for a condition benefited by stimulating hair growth which method comprises administering to said mammalian subject in need of such treatment an effective amount of a compound that inhibits the activity of NF-κB or that inhibits proteasomal activity or that inhibits production of these proteins.

26. The method of claim 25, wherein said compound inhibits proteasomal activity or inhibits production of proteasome proteins.

27. The method of claim 26, wherein the compound inhibits the trypsin-like or PGPH activity of the proteasome.

28. The method of claim 25, wherein the compound is lactacystin or a peptidyl aldehyde.

29. A pharmaceutical composition for treating bone disorders, dental pathological conditions or degenerative joint conditions, which composition comprises a compound that inhibits the activity of NF-κB or that inhibits proteasomal activity or that inhibits production of these proteins, in the compound does not inhibit the isoprenoid pathway.

30. The pharmaceutical composition of claim 29, wherein the compound inhibits proteasomal activity or inhibits production of proteasomal proteins.

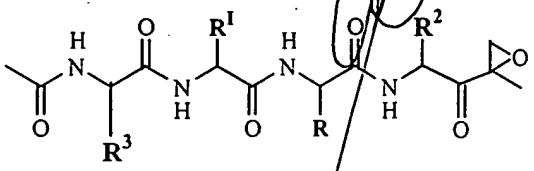
31. The pharmaceutical composition of claim 30, wherein the compound inhibits the chymotrypsin-like activity of the proteasome.

32. The pharmaceutical composition of claim 31, wherein the compound is a peptide having at least 3 amino acids and a c-terminal functional group that reacts with the threonine residue of the chymotrypsin-like catalytic site of the proteasome.

33. The pharmaceutical composition of claim 32, wherein the c-terminal functional group is selected from the group consisting of an epoxide, a $-B(OR)_2$ group, a $-S(OR)_2$ group and a -SOOR group, wherein R is H, an alkyl (C_{1-6}) or an aryl (C_{1-6}).

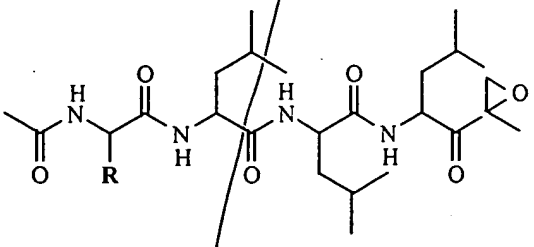
34. The pharmaceutical composition of claim 32, wherein the peptide is a peptide α', β'-epoxyketone.

35. The pharmaceutical composition of claim 34, wherein the peptide α', β'-epoxyketone has the following formula:

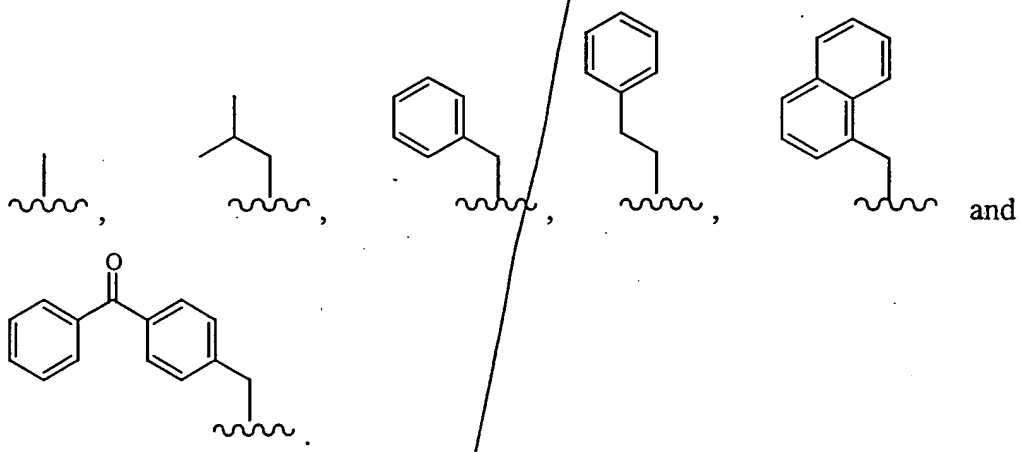


wherein each of R, R^I, R^2 and R^3 is a hydrophophic substituent.

36. The pharmaceutical composition of claim 34, wherein the peptide α', β'-epoxyketone has the following formula:

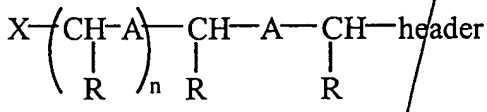


wherein R is selected from the group consisting of



and

37. The pharmaceutical composition of claim 31, wherein the compound has the following formula:



,

wherein the header reacts irreversibly with the catalytic chymotrypsin site of the proteasome;

A is independently CO-NH or isostereomer thereof;

R is independently a hydrocarbyl;

X is a polar group; and

n = 0-2.

38. The pharmaceutical composition of claim 29, wherein the compound is lactacystin, a peptidyl aldehyde, PTX, epoxomicin or PSI eopxide.

39. A pharmaceutical composition for treating a condition benefited by stimulating hair growth, which composition comprises a compound that inhibits the activity of NF-κB or that inhibits proteasomal activity or that inhibits production of these proteins.

40. The pharmaceutical composition of claim 39, wherein the compound inhibits proteasomal activity or inhibits production of proteasomal proteins.

41. The pharmaceutical composition of claim 40, wherein the compound inhibits the trypsin-like or PGPH activity of the proteasome.

42. The pharmaceutical composition of claim 39, wherein the compound is lactacystin or a peptidyl aldehyde.

43. A method to identify a compound which enhances bone growth or stimulates hair growth, which method comprises subjecting said compound to an assay for determining its ability to inhibit NF-κB activity, whereby a compound which inhibits the activity of NF-κB is identified as a compound which enhances bone growth or stimulates hair growth; or

subjecting said compound to an assay for determining its ability to inhibit the production of NF-κB, whereby a compound which inhibits the production of NF-κB is identified as a compound which enhances bone growth or stimulates hair growth; or

subjecting a candidate compound to an assay to assess its ability to inhibit proteasomal activity, whereby a compound which inhibits proteasomal activity is identified as a compound that enhances bone growth or stimulates hair growth; or

subjecting a candidate compound to an assay to assess its ability to inhibit the production of enzymes with proteasomal activity, whereby a compound which inhibits the production of enzymes with proteasomal activity is identified as a compound that enhances bone growth or stimulates hair growth.

44. The method of claim 43, wherein the proteasomal activity to be inhibited is selected from the group consisting of the chymotrypsin-like activity, the trypsin-like activity, the PGPH activity and a combination thereof.

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